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(54) Title: METHOD AND COMPOSITION FOR THE TREATMENT OF DIABETIC NEUROPATHY

(57) Abstract: Compositions and a method for the treatment of diabetic neuropathy are disclosed. The compositions comprise a mixture of a compound that promotes synthesis of nerve growth factor, an aldose reductase inhibitor and an antioxidant, optionally formulated in a pharmaceutically acceptable carrier. This combination of active agents provides significant, effective relief of the symptoms of diabetic neuropathy, as well as at least partial recovery of lost neurological function in some cases. In addition, the compositions of the present invention, when used in effective amounts to treat diabetic neuropathy, do not exhibit the severe side effects of many prior art compositions proposed for treatment of this ailment. In a second aspect, a method for the administration of a composition in accordance with the present invention for the treatment of diabetic neuropathy is disclosed. In the method, an effective amount of the composition of the invention is administered over a period of time sufficient to provide the beneficial effects of relief from the symptoms of diabetic neuropathy, as well as at least some recovery of the damaged nerve tissues.

COMPOSITIONS AND METHODS FOR THE TREATMENT OF DIABETIC NEUROPATHY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a composition and a method for the treatment of diabetic neuropathy. More particularly, the present invention relates to a composition including a combination of ingredients, which provide a surprising degree of effective relief from symptoms of diabetic neuropathy and to a method for using the compositions to treat diabetic neuropathy.

2. Description of the Prior Art

Diabetes mellitus is a common disease that is usually classified into insulin-dependent and non-insulin dependent types. Both types may be managed by diet, in combination with insulin in the first type and a variety of drugs in the second type. However, while conscientious patients and doctors can usually manage the changes in blood glucose associated with diabetes reasonably satisfactorily, this does not prevent long term damage to many tissues as a result of the disease. This damage may take many forms but the major types are damage to the eyes (retinopathy), nerves (neuropathy), kidneys (nephropathy) and cardiovascular system.

There are many approaches to reducing or preventing these forms of damage, which are collectively known as the long-term complications of diabetes. One approach is based on damage that results from over-production of the glucose metabolite, sorbitol, in the cells of the body. Glucose can be converted to sorbitol by the enzyme aldose reductase. High levels of sorbitol may be among the causes of diabetic complications such as diabetic neuropathy. As a result, a number of pharmaceutical companies have been developing aldose reductase inhibitors for the purpose of reducing diabetic neuropathy.

It has been established that a wide variety of flavanoids are effective inhibitors of aldose reductase, including such flavanoids as quercetin, quercitrin and myrecetrin.

However, U.S. Patent No. 4,232,040 discloses that despite the fact that these flavanoids have been shown in *in vitro* studies to be among the most potent flavanoids for aldose reductase inhibition, a need exists for aldose reductase inhibitors that can be used more effectively and in lower doses than these flavanoids.

In fact, numerous patents are devoted to the goal of developing improved aldose reductase inhibitors. Among these patents are U.S. Patent Nos. 6,069,168; 5,011,840; 4,210,667; 4,147,795; 5,866,578; and 5,561,110. Numerous other patents exist which relate to aldose reductase inhibitors.

Another approach to the treatment of diabetic neuropathy is disclosed in U.S. Patent No. 5,840,736 (Zelle et al.). In this method, pharmaceutical compositions are disclosed for stimulating the growth of neurites in nerve cells. The compositions include a neurotrophic amount of a compound and a nerve growth factor. These compositions may be administered in a number of ways including orally and topically.

Still another approach to the treatment of neuropathy is disclosed in U.S. Patent No. 5,550,249 (Della Ville et al.). In this approach, compositions suitable for treatment of vitamin H deficiencies are administered for the treatment of neuropathy. This patent relates to biotin salts with alkanolamines. The compositions may be administered orally, parenterally or topically.

U.S. Patent No. 5,665,360 (Mann) relates to the treatment of peripheral neuropathies associated with diabetes mellitus by periodic topical application of a composition containing capsicum oleoresin as the active ingredient. When applied to the skin of the affected area, pain and burning associated with the neuropathy are said to be reduced. However, capsicum oleoresin has been shown to kill nerve endings in some cases and thus this composition suffers from this disadvantage.

U.S. Patent No. 5,981,594 (Okamoto et al.) relates to a method of treatment of diabetic neuropathy using combined administration of a formulation including as an active ingredient, a prostaglandin I derivative with an anti-diabetic agent in order to improve nerve conduction velocities. Suitable anti-diabetic agents include oral hypoglycemic agents and insulin.

The Okamoto patent also contains a detailed discussion of the various types of neuropathy that may be associated with diabetes. According to this patent, nerve conduction velocity (NCV) is the most widely used method of objectively evaluating the severity of diabetic neuropathy. This patent also mentions that current methods of treating diabetic neuropathy such as dietetic therapy, administration of insulin, aldose reductase inhibitors or aminoguanidine to improve abnormal glucose metabolism, and administration of troglitazone or agents for the improvement of blood flow have been tested but found to be insufficient when a single drug was used. Also, according to this patent, methods of treatment by combined use of different therapeutic agents which have different functions had yet to be established. The patent concludes that combined drug therapies for diabetic neuropathy, aiming at recovering once reduced nerve conduction velocity, have not yet been confirmed.

There remains a need in the art for an effective treatment for diabetic neuropathy that does not suffer from the disadvantage that it causes severe side effects, as do many aldose reductase inhibitors, for example.

Accordingly, it is the primary object of the present invention to provide a composition that is effective for the treatment of diabetic neuropathy.

It is another object of the present invention to provide a composition for the treatment of diabetic neuropathy that does not cause severe side effects in the patient treated with the composition.

These and other objects of the present invention will be apparent from the summary and detailed descriptions of the invention that follow.

SUMMARY OF THE INVENTION

In a first aspect, the present invention relates to a composition for the treatment of diabetic neuropathy. The composition includes a mixture of a compound that promotes synthesis of nerve growth factor, an aldose reductase inhibitor and an antioxidant, optionally formulated in a pharmaceutically acceptable carrier. It has been found that this combination of active agents provides significant, effective relief of symptoms of diabetic

neuropathy, as well as at least partial recovery of lost neurological function in some cases. In view of the consensus in the art that combinations of various active agents have not been demonstrated to be effective for the treatment of diabetic neuropathy, the present invention provides a surprising and unexpected effect. In addition, the composition of the present invention, when used in effective amounts to treat diabetic neuropathy, does not exhibit the severe side effects of many prior art compositions proposed for treatment of this ailment.

In a second aspect, the present invention relates to a method for the administration of a composition in accordance with the present invention for the treatment of diabetic neuropathy. In the method, an effective amount of the composition of the invention is administered over a period of time sufficient to provide the beneficial effects of relief from the symptoms.

In a third aspect, the present invention relates to a pharmaceutically acceptable carrier for a topical composition that provides excellent dispersions and/or solutions of active ingredients and good penetration through the skin to the areas to be treated. The carrier for a topical composition may also include one or more materials that provide beneficial properties to the skin since many sufferers from diabetic neuropathy develop skin problems such as ulcers, lesions or cell damage.

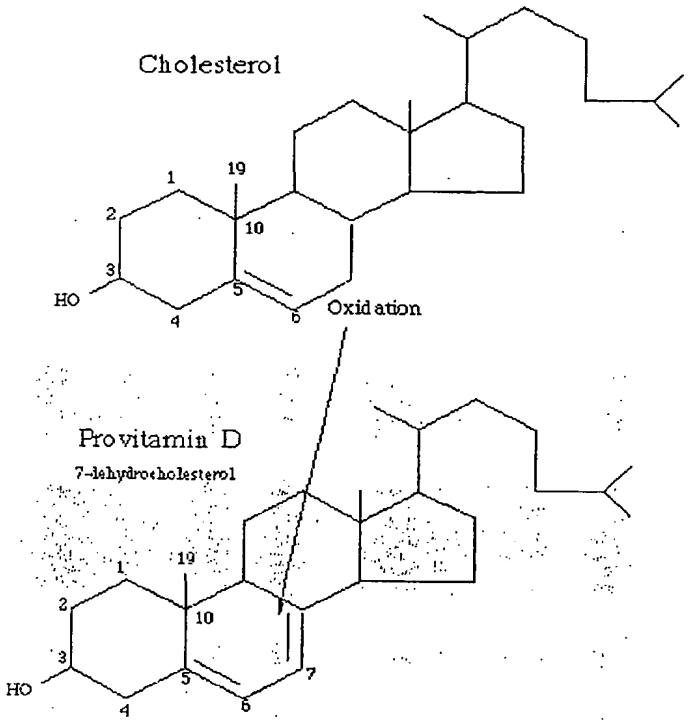
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In a first aspect, the present invention relates to a composition for the treatment of diabetic neuropathy. The composition includes at least a compound that promotes synthesis of nerve growth factor, an aldose reductase inhibitor and an antioxidant.

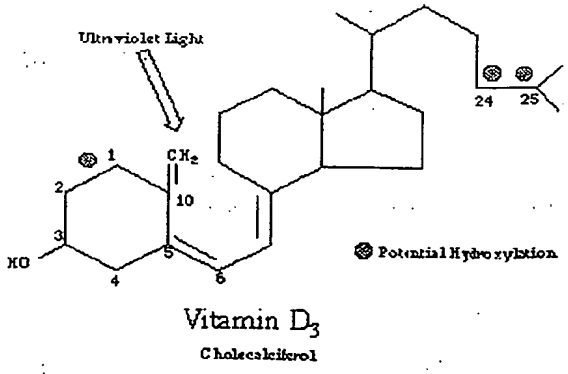
The compound that promotes synthesis of nerve growth factor may be selected from suitable compounds that have been shown to have this activity. Suitable compounds that promote synthesis of nerve growth factor are those that do not induce significant, adverse side effects when administered to a patient in amounts that promote synthesis of nerve growth factor, and which do not react with one or more of the ingredients of the compositions of the invention thereby resulting in a substantial loss of activity of one or more active ingredients. Preferred compounds for promoting synthesis of nerve growth

factor are those that occur naturally in the human body and/or materials obtained from plants, animals or derivatives thereof, which may be administered to humans without significant, adverse side effects in the amounts used.

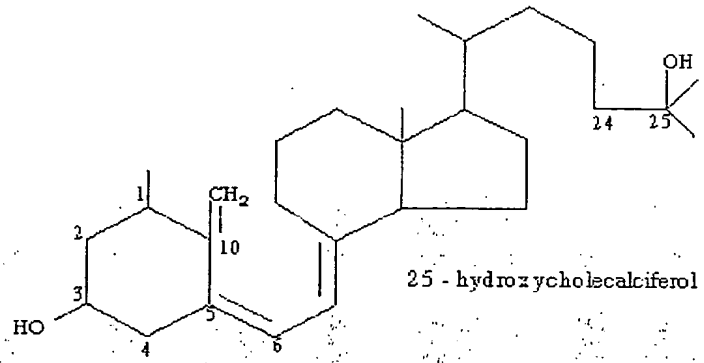
Exemplary compounds that promote synthesis of nerve growth factor useful in the present invention include vitamin D_3, vitamin D_3 analogs, compounds that may be converted or metabolized into vitamin D_3 in the human body, and metabolites thereof. Exemplary compounds that may be converted or metabolized into a vitamin D_3 include certain cholesterols, which are illustrated below. Such cholesterols may be converted into Provitamin D when a hydrogen atom is removed from the number 7 carbon atom, to thereby form a double bond with the number 8 carbon atom, in the second, or 'B' ring of the cholesterol molecule. The cholesterol is 'oxidized' (that is, an electron is removed with the hydrogen atom), so that the double bond is a consequence of two electrons shared mutually by the numbers 7 and 8 carbon atoms of the cholesterol.



Provitamin D may be converted to Vitamin D_3 in human body by the action of ultraviolet light through the skin. In this reaction, the B ring of the sterol molecule is opened.

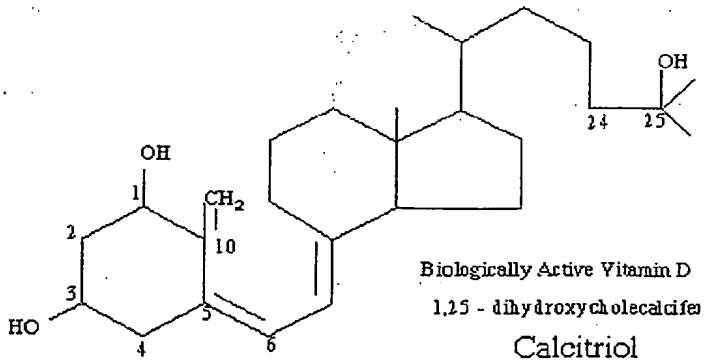


Cholecalciferol, which is Vitamin D_3, may be further converted into another vitamin D intermediate, 25-hydroxycholecalciferol, in the liver by mitochondrial hydroxylase, in the presence of NADPH, and molecular oxygen.



25 - hydroxycholecalciferol

When a more active vitamin D_3 is required, 25-hydroxycholecalciferol is transported to the kidney where a new hydrolase enzyme is synthesized. This enzyme introduces another hydroxyl group at position 1, and the bioactive form of Vitamin D_3, calcitriol, is produced.



Biologically Active Vitamin D

1,25 - dihydroxycholecalcife

Calcitriol

Exemplary vitamin D_3 analogs include 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene. Exemplary vitamin D_3 metabolites include 1, 25-dihydroxyvitamin D_3. Also, pharmaceutically

acceptable salts of the compounds that promote synthesis of nerve growth factor may be employed. The most preferred compound that promotes synthesis of nerve growth factor is vitamin D_3.

The preferred compounds that promote the synthesis of nerve growth factor may, in addition to this activity, also function to prevent neurotrophic deficits. This additional effect of the preferred compounds may also contribute to the overall beneficial effect of the composition of the present invention.

In order to formulate the compound that promotes synthesis of nerve growth factor in the composition of the present invention, it may be necessary to use a dispersant. Suitable dispersants are known to persons skilled in the art. A particularly suitable dispersant for the compounds that promote synthesis of nerve growth factor is corn oil. Corn oil also has the advantage that it is a natural product. The amount of corn oil used is an amount sufficient to disperse the compound that promotes synthesis of nerve growth factor.

The second ingredient of the composition of the present invention is an aldose reductase inhibitor. Numerous suitable aldose reductase inhibitors are known to persons skilled in the art. Again, suitable aldose reductase inhibitors are those that do not induce significant, adverse side effects when administered to a patient in an amount effective for aldose reductase inhibition, and which do not react with one or more of the ingredients of the composition of the present invention thereby resulting in a substantial loss of activity of one or more active ingredients of the composition. Preferred aldose reductase inhibitors are those that occur naturally in the human body and/or materials obtained from plants, animals, or derivatives thereof, which may be administered to humans without significant, adverse side effects in the amounts used.

As mentioned above, numerous aldose reductase inhibitors are known to persons skilled in the art. However, significant adverse side effects are associated with the use of many aldose reductase inhibitors in humans. Thus, it is important to select one or more aldose reductase inhibitors for use in the compositions of the present invention based on minimizing the risk associated with use of the aldose reductase inhibitor taking into account

the amount of that particular inhibitor that must be employed to achieve the desired level of aldose reductase inhibition. Different aldose reductase inhibitors exhibit different levels of inhibition. With this in mind, the preferred aldose reductase inhibitors for use in the compositions of the present invention are flavonoids and flavonoid derivatives. Exemplary aldose reductase inhibitors include (-)-epigallocatechin; (-)-epigallocatechin-gallate; 1,2,3,6-tetra-o-gallyol-β-d-glucose; 2'o-acetylacetoside; 3,3',4-tri-o-methyl-ellagic acid; 6,3',4'-trihydroxy-5,7,8-trimethoxyflavone; 6-hydroxy-luteolin; 6-hydroxykaempferol-3,6-dimethyl ether; 7-o-acetyl-8-epi-loganic acid; acacetin; acetoside; acetyl trisulfate quercetin; amentoflavone; apigenin; apiin; astragalin; avicularin; axillarin; baicalein; brazilin; brevifolin carboxylic acid; caryophyllene; chrysin-5,7-dihydroxyflavone; chrysoeriol; chrysosplenol; chrysosplenoside-a; chrysosplenoside-d; cosmosiin; δ-cadinene; dimethylmussaenoside; diacerylcirsimaritin; diosmetin; dosmetin; ellagic acid; ebinin; ethyl brevifolin carboxylate; flavocannibiside; flavosativaside; genistein; gossypetin-8-glucoside; haematoxylin; hesperidine; hispiduloside; hyperin; indole; iridine; isoliquiritigenin; isoliquiritin; isoquercitrin; jionoside; juglanin; kaempferol-3-rhamnoside; kaempferol-3-neohesperidoside; kolaviron; licuraside; linariin; linarin; lonicerin; luteolin; luetolin-7-glucoside; luteolin-7-glucoside; luetolin-7-glucoronide; macrocarpal-a; macrocarpal-b; macrocarpal-d; macrocarpal-g; maniflavone; methy scutellarein; naringenin; naringin; nelumboside; nepetin; nepetrin; nerolidol; oxyayanin-a; pectolinarigenin; pectolinarin; quercetagetin; quercetin; quercimertrin; quercitrin; quercitryl-2'' acetate; reynoutrin; rhamnetin; rhoifolin; rutin; scutellarein; sideritoflavone; sophoricoside; sorbarin; spiraeoside; trifolin; vitexin; and wogonin.

The most preferred flavonoid and/or flavonoid derivative aldose reductase inhibitors are quercetin, quercitrin, myricetin, kaempferol and myrecetrin since these compounds exhibit a high level of aldose reductase inhibition in combination with a relatively low toxicity. Also, pharmaceutically acceptable salts of these aldose reductase inhibitors may be employed. The particular aldose reductase inhibitor included in the composition may be determined by factors such as toxicity, bioavailability, solubility and dispersability, among others.

The flavonoids and flavonoid derivatives are also preferred since some of these compounds may provide additional beneficial effects in the composition of the present invention. For example, quercetin may act as a chelator for transition metals that some studies have linked to certain symptoms of diabetic neuropathy.

Flavonoids may also have some anti-inflammatory activity and/or may help stabilize cell membranes, both of which activities may be beneficial in the treatment of diabetic neuropathy. For example, quercetin may also have an antioxidative and anticlastogentic effect. In addition, some of the flavonoids and flavonoid derivatives may act as a radical scavenger to scavenge free radicals such as hydroxyl radicals to enhance further enhance the antioxidant effect of the composition of the present invention.

Another active ingredient in the composition of the present invention is the antioxidant. The antioxidant may be a single compound or a mixture of two or more compounds. Also, the antioxidant may include one or more compounds that provide additional beneficial effects beyond the antioxidant activity, such as aldose reductase inhibition.

Compounds which may be used as antioxidants are those which exhibit antioxidant activity when administered without causing any severe adverse side affects when used in an amount effective to provide sufficient antioxidant activity, and which do not react with one or more of the ingredients of the composition of the present invention thereby resulting in a substantial loss of activity of one or more active ingredients. Preferred antioxidants are those that occur naturally in the human body and/or materials obtained from plants or animals which may be administered to humans without significant, adverse side effects in the amounts used, or derivatives thereof.

Preferred antioxidants are selected from ascorbyl palmitate, ascorbic acid (vitamin C), vitamin A, vitamin E acetate, α-lipoic acid, especially DL- α-lipoic acid, coenzyme Q10, glutathione, (-)-epigallocatechin-3-gallate, catechin, galangin, rutin, luteolin, morin, fisetin, silymarin, apigenin, gingkolides, hesperitin, cyanidin, citrin, curcuminoid and derivatives thereof which exhibit antioxidant activity.

Even more preferably, mixtures of two or more antioxidants are employed in the composition of the present invention. Particularly preferred antioxidant mixtures are mixtures of ascorbyl palmitate with one or more of vitamin A, vitamin E acetate and α-lipoic acid, especially DL-α-lipoic acid. Derivatives of one or more of these compounds, which exhibit antioxidant activity when administered in the compositions of the present invention may also be employed. The antioxidants may also be used in the form of their pharmaceutically acceptable salts and this may be preferred in some cases to increase solubility or dispersability, to reduce adverse side effects, etc.

By "derivatives" is meant structurally similar compounds that exhibit antioxidant activity and contain at least one significant, common structural element with the compound from which it is derived, which common structural element provides antioxidant activity.

In another preferred embodiment, the antioxidant used in the composition of the present invention may be partially or completely replaced with an amount of one or more antioxidant enzymes having a comparable level of activity. The antioxidant enzymes useful in the present invention are those capable of scavenging radicals, promoting radical scavengers or preventing radical formation. In one more preferred embodiment, the antioxidant enzyme used in the present invention is skin absorbable. The preferred antioxidant enzymes for use in the present invention include superoxide dismutase, catalase, glutathione peroxidase, methionine reductase and equivalents thereof. These antioxidant enzymes may prevent the formation of free radicals or scavenge the formed free radicals to prevent cell damage. In addition, one or more of these antioxidant enzymes may act synergistically with one or more of the antioxidants in the composition to scavenge free radicals more effectively and thereby help to prevent cell damage in the skin.

The antioxidants used in the composition of the present invention are preferably selected not only for their antioxidant activity, but also based on other beneficial effects that particular compounds may provide. For example, ascorbyl palmitate not only has antioxidant activity, but also may act as an aldose reductase inhibitor and may help prevent degradation of nitric oxide (NO) and thus is a particularly preferred antioxidant for the present invention. Similarly, vitamin E may also help prevent degradation of nitric oxide

and is thus a preferred antioxidant. A racemic mixture of α-lipoic acid not only has a strong antioxidant activity but also has a recycling effect on vitamins C and E, and thus is a particularly preferred antioxidant for the present invention. In addition, α-lipoic acid can function in both lipid and non-lipid environments. Similarly, vitamin E may also contribute to an anticancer effect and provide a further beneficial effect on the skin and is thus a preferred antioxidant in one embodiment of the present invention. Vitamin A (retinol or retinyl ester) may also have anticancer effects. Vitamin A is also a fat-soluble material and thus is preferred for use due to this additional beneficial property. However, due to its solubility characteristics, vitamin A may need to be formulated in a suitable dispersant such as corn oil in much the same manner as vitamin D_3 as described above.

Preferably, the antioxidant used in the composition of the present invention includes a combination of effective amounts of vitamin A, vitamin C or its ester, vitamin E and α-lipoic acid to achieve, in addition to the antioxidant effect, the beneficial effect of recycling vitamin C or its ester and vitamin E by α-lipoic acid.

In another preferred embodiment, antioxidant mixtures including ascorbyl palmitate with one or both of vitamin A and vitamin E as tocopherols or vitamin E as mixed tocopherols are employed in the composition of the present invention. Most preferably, all-natural vitamin E tocopherols are employed. The antioxidants may also be used in the form of their pharmaceutically acceptable salts and this may be preferred in some cases to increase solubility or dispersability, to reduce adverse side effects, to increase bioavailability, etc.

In a more preferred embodiment, both quercetin and ascorbyl palmitate are included in the composition of the present invention because there seems to be an enhanced anti-oxidative effect of the combination of quercetin and ascorbyl palmitate.

The antioxidant component of the composition is used in an amount effective to provide significant antioxidant activity when administered to a patient in the composition of the present invention.

Preferably, vitamins A and D_3 may be formulated in a single corn oil dispersion. Generally, each cubic centimeter (cc) of the corn oil dispersion of vitamins A and D_3 used

in the present invention may contain 500,000 to 2,000,000 IU of vitamin A and 50,000 to 200,000 IU of vitamin D_3. Preferably, every cc of the corn oil dispersion of vitamins A and D_3 used in the present invention may contain 800,000 to 1,200,000 IU of vitamin A and 80,000 IU to 120,000 IU of vitamin D_3. The most preferred amounts of vitamins A and D_3 employed in the composition of the invention are 1,000,000 IU and 100,000 IU, respectively.

The aldose reductase inhibitor is used in an amount of 0.04 to 40 grams, per gram of the antioxidant in the composition. More preferably, the aldose reductase inhibitor is employed in an amount of 0.17 to 15 grams and, most preferably, 0.4 to 4 grams of the aldose reductase inhibitor, per gram of the total antioxidant in the composition, is employed. The ratio of the amount of the compound that promotes synthesis of nerve growth factor to the amount of antioxidant employed in the compositions of the present invention is from 200 IU per gram of antioxidant to 3 million IU, per gram of antioxidant. More preferably, 1800 IU to 1 million IU, per gram of antioxidant, and, most preferably 5000 IU to 200,000 IU, per gram of antioxidant, of the compound that promotes synthesis of nerve growth factor is employed.

The compositions of the present invention may provide one or more of the following beneficial effects to a patient when administered in effective amounts: relief of pain, burning, tingling, electrical sensations and/or hyperalgesia, increased microcirculation, nitric oxide stabilization, promotion of healing of skin ulcers and lesions, protein kinase C inhibition, decreased oxidative stress, anti-inflammation, blockage of the formation of leukotrienes, stabilization of cell membranes, and promotion of the synthesis of nerve growth factor.

Other compounds may also be included in the composition of the present invention to provide additional benefits. Desirable additional beneficial properties for the other compounds useful in the composition of the present invention include absorbability when applied topically, aldose reductase inhibition, antioxidant properties, free radical scavenging, transition metal chelation, nitric oxide stabilization, and anti-inflammatory

activity, which may have a beneficial effect on the pain of other related disorders such as fibromyalgia.

In a second aspect, the present invention provides a method for the treatment of diabetic neuropathy involving the administration of a composition of the present invention by a method of administration selected from the group consisting of topical administration, oral administration, parenteral administration, via an implanted reservoir or by inhalation. The composition is administered to a patient that suffers from diabetic neuropathy. In the method, an effective amount of the composition of the invention is administered one to six times daily as needed to relieve pain and other symptoms of the diabetic neuropathy.

The compositions of the present invention may be administered topically, orally, parenterally, by inhalation or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

In one embodiment, the composition is administered orally, intraperitoneally or intraveneously. Preferably, when administered orally, intraperitoneally or intravenously, the composition is administered two to four times daily, as needed for pain. A sufficient amount should be administered to provide one or more of the beneficial effects of the compositions described above. The method initially treats acute symptoms but may be continued indefinitely to relieve pain, prevent symptoms from returning and possibly restore some nerve and/or skin function.

In this embodiment, when the composition of the present invention is administered to a patient orally, intraperitoneally or intraveneously, the compound that promotes synthesis of nerve growth factor is used in an effective amount of 6-14.3 IU per kg. of body weight of the patient for each administration. More preferably, the compound that promotes synthesis of nerve growth factor is employed in an amount of 8-14.3 IU per kg body weight of the patient, and most preferably, an amount of 10-13 IU is employed per kg of body weight of the patient.

In this embodiment, the aldose reductase inhibitor is used in an amount that provides substantially the same level of aldose reductase inhibition as 13-22 mg./kg. body weight of the patient, per day, of quercetin. More preferably, the aldose reductase inhibitor is employed in an amount that provides substantially the same level of aldose reductase inhibition as 17.2-21.4 mg./ kg. body weight of the patient, per day, of quercetin, and, most preferably, an amount that provides substantially the same level of aldose reductase inhibition as 18-21 mg./kg. body weight of the patient, per day, of quercetin, is employed.

In this embodiment, ascorbyl palmitate may be used in an amount of 11-29 mg./kg body weight of the patient, per day. More preferably, ascorbyl palmitate is used in an amount of 14.3-28.6 mg./kg body weight of the patient per day. Most preferably ascorbyl palmitate is used in an amount of 16-26 mg./ kg body weight of the patient, per day.

When vitamin E is employed as mixed tocopherols, an amount of 4-12 IU per kg body weight of the patient, per day, may be employed. More preferably, 5.7-11.4 IU per kg body weight of the patient, per day, may be employed. Most preferably, 6-10 IU per kg body weight of the patient, per day, may be employed.

In this embodiment, when vitamin A is employed, an amount of 170-360 IU per kg body weight of the patient, per day, is employed. More preferably, an amount of 214.3-357.1 IU per kg body weight of the patient, per day, is employed. Most preferably, an amount of 220-340 IU per kg body weight of the patient, per day, is employed.

The compositions of the present invention may be formulated using the active agents including a compound that promotes the synthesis of nerve growth factor, an aldose reductase inhibitor and an antioxidant; and one or more of the optional ingredients described below or; more preferably, are formulated with a pharmaceutically acceptable carrier. The active or non-carrier ingredients may be combined with the carrier materials to produce a particular dosage form, or be customized for a particular treatment regimen. Thus, the amount of each ingredient may vary depending on such factors as the particular mode of administration, the activity of the particular active agents employed, the age, bodyweight, general health, sex, and diet of the patient, time of administration, rate of

excretion, the combination of active agents, or the severity of the illness, among other potential factors.

Sterile injectable forms of the composition of the invention may be in the form of an aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and/or suspending agents, if needed. The sterile injectable preparation may also be in the form of a solution or suspension in a non-toxic, parenterally acceptable diluent or solvent. The vehicles or solvents that may be employed include water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may also be employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids such as oleic acid and its glyceride derivatives that are useful in the preparation of injectables. Also useful are natural, pharmaceutically acceptable oils such as olive oil or castor oil, especially when polyethoxylated. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

For parenteral administration, non-sterile solutions of the active agents in sesame or peanut oil or in aqueous propylene glycol or N,N-dimethylformamide may be employed. Aqueous solutions may include a suitable buffering agent and are preferably rendered isotonic via use of saline or glucose.

The compositions of the present invention may also be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, lozenges, troches, hard candies, powders, sprays, elixirs, syrups, and suspensions or solutions.

In the case of tablets for oral use, suitable pharmaceutically acceptable carriers include lactose and corn starch. Lubricating agents may also be added to the tablets, including, for example, magnesium stearate, sodium lauryl sulfate and talc. Tablets may also contain excipients such as sodium citrate, calcium carbonate and calcium phosphate. Disintegrants such as starch, alginic acid and complex silicates, may also be employed. Tablets may also include binding agents such as polyvinylpyrrolidone, gelatin and gum acacia.

When the composition of the invention is administered in capsule form, it may be used with or without diluents. For capsules, useful diluents include lactose and dried cornstarch. When suspensions are employed, emulsifying and/or suspending agents may be employed in the suspensions. In addition, solid compositions including one or more of the ingredients of the tablets described above may be employed in soft and hard gelatin capsules.

The compositions of the present invention may also be administered by nasal aerosol or by inhalation. Such compositions may be prepared using well-known techniques. For this method of administration, suitable carriers include saline and/or other conventional solubilizing or dispersion agents, optionally formulated with one or more preservatives, absorption promoters to enhance bioavailability, and/or fluorocarbons.

In general, the active ingredients, which include the compound that promotes the synthesis of nerve growth factor, the aldose reductase inhibitor and the antioxidant, will make up from 0.5-90% by weight of the total composition to provide the desired unit dosage. The body weight dosages given above are based on a patient having a body weight of 70 kg, which is the accepted standard patient for the purpose of clinical trials. Dosages may be administered 1-10 times per day, more preferably 2-8 times per day and most preferably, 4-8 times per day. The appropriate unit dosage may be determined by dividing the daily dosage by the number of unit doses per day, which will be employed in the particular treatment regimen for a specific patient.

Other materials which may optionally be included in the oral, parenteral, injectable or inhalable composition of the present invention include inositol, other B-complex vitamins, and anti-inflammatories. Also, ingredients such as sweeteners, flavorants, coloring agents, dyes, and diluents such as water, ethanol, propylene glycol, glycerin and various combinations thereof may be included in the compositions of the present invention.

In another preferred embodiment, the method of the present invention involves the topical application of a composition of the present invention to an area of the skin in the vicinity of tissue that suffers from diabetic neuropathy. In particular, the present invention

is useful on the patients' extremities such as the fingers, toes, hands and feet where diabetic neuropathy is often the most pervasive.

In the topical embodiment, the topical composition preferably includes a pharmaceutically acceptable topical carrier. In the method, a suitable amount of the topical composition of the invention is applied one to six times daily as needed to an area of the skin in the vicinity of tissue that suffers from diabetic neuropathy in order to relieve pain and other symptoms of the diabetic neuropathy. Preferably, the topical composition is applied two to four times daily, as needed for pain. In the preferred method, a sufficient amount of the topical composition is applied to cover the afflicted area with a thin layer of the composition and the composition is rubbed into the skin until little or no residue remains on the skin. Treatment initially addresses acute symptoms but may be continued indefinitely to relieve pain, prevent symptoms of diabetic neuropathy from returning and possibly restore some nerve and/or skin function.

The topical embodiment of the method of the present invention may provide one or more of the beneficial effects described above for the composition of the invention. In addition, the method of the present invention employing the topical composition may provide some additional beneficial effects due to one or more of the ingredients contained in the pharmaceutically acceptable topical carrier as described in more detail below.

The pharmaceutically acceptable topical carrier of the present invention is suitable for use as a carrier for a topical composition wherein the active ingredients are dissolved, dispersed and/or suspended in the composition. The topical carrier of the present invention contains at least a hydrophilic ointment base, panthenol or a panthenol derivative and one or more dispersants, if needed to disperse one or more insoluble or partially insoluble active agents in the carrier. Another preferred carrier of the present invention employs hydroxymethyl cellulose as the carrier material.

Yet another preferred pharmaceutically acceptable carrier may include a solution of an acrylic copolymer in a non-aqueous solvent system, which mainly contains polyethylene glycol such as methoxy polyethylene glycol 550 (MPEG). A particular preferred MPEG is SENTRY CARBOWAX MPEG 550 sold by Union Carbide, which is a

food/pharmaceutical/cosmetic grade material. Polyethylene glycols are generally non-toxic, water-soluble polymers that are fully biodegradable. In the solution, the acrylic copolymer would preferably be present in a concentration range of 3-6 % by weight. Preferably, the acrylic copolymer has a molecular weight of more than 20,000. More preferably, the acrylic copolymer has a molecular weight of more than 100,000, so that the acrylic copolymer will not be substantially absorbed by the human body through the skin.

Suitable hydrophilic ointment bases are known to persons skilled in the art. Exemplary hydrophilic ointment bases suitable for use in the present invention are non-U.S.P. hydrophilic ointment bases such as those made by Fougera, Inc. Sufficient hydrophilic ointment base is employed to act as a carrier for the active ingredients of the composition. Typically the hydrophilic ointment base will make up more than 80% of the total composition and more preferably 80-90% of the composition is the hydrophilic ointment base. The hydrophilic ointment base functions as a carrier and preferably enhances penetration of the active agents into the skin.

The panthenol or panthenol derivatives useful in the present invention include at least D-panthenol, DL-panthenol and mixtures thereof. This component of the topical carrier has skin moisturizing properties, acts as a quick, deep penetrating component of the carrier that helps deliver the active agents through the skin to the area to be treated and imparts a healing effect to damaged tissue. The amount of panthenol or panthenol derivative to be employed is from 0.25 to 10 weight percent, more preferably, from 0.5 to 5 weight percent, and, most preferably, from 1 to 2 weight percent is employed, based on the total weight of the topical composition.

The topical carrier of the present invention may also include additional ingredients known to persons skilled in the art such as other carrier materials, moisturizers, humectants, emollients dispersants, radiation blocking compounds, particularly UV-blockers, as well as other suitable materials that do not have a significant adverse effect on the activity of the topical composition in the amount used. Preferred additional ingredients for inclusion in the carrier are sodium acid phosphate as a moisturizer, witch hazel extract as a carrier, glycerine as a humectant, apricot kernal oil as an emollient, and corn oil as a dispersant.

Other materials that may optionally be included in the topical composition of the present invention include inositol, other B-complex vitamins, and anti-inflammatory agents. The composition of the present invention may also be employed to facilitate wound healing, for the treatment of skin cancer and/or one or more symptoms thereof, or as a composition for protecting skin from the harmful effects of radiation such as radiation breakdown.

The topical composition of the present invention is preferably made by cold compounding. This may be an important feature of the invention since one or more of the compounds employed in the topical composition are known to be sensitive to heat or other types of energy and thus the activity of the composition may be detrimentally affected as a result of formulating the composition in other ways. Thus, the ingredients of the topical composition the present invention are preferably mixed together, without heating, using a sufficient amount of the topical carrier to provide a substantially homogeneous cream or ointment. It may be necessary to dissolve, disperse or suspend one or more of the ingredients prior to cold compounding in order to ensure substantially homogeneous distribution of one or more of the ingredients in the composition.

Every kilogram of a preferred topical composition of the present invention may include: 10,000 to 3 million IU of the compound that promotes synthesis of nerve growth factor, 2 to 40 grams of aldose reductase inhibitor, 1 to 50 grams of antioxidants, and other suitable ingredients such as topical carriers.

A more preferred topical composition of the invention can be made using the following ingredients, all based on use of one pound of hydrophilic ointment base. 25-35 cc of a 50% aqueous solution of sodium acid phosphate moisturizing agent, 5-10 cc of D- or DL-panthenol, 5-10 cc of glycerine, 1-3 cc of apricot kernal oil, 3-5 cc of a dispersion of vitamins A and D_3 in a corn oil base, 10-20 cc of witch hazel extract, 0.5-2 cc of vitamin E acetate, 2-4 grams of ascorbyl palmitate and 4-8 grams of quercetin powder. Optionally, one or more of the glycerin, witch hazel extract, vitamins A and E and/or the ascorbyl palmitate can be reduced or eliminated from a particular composition, if desirable, or larger

amounts of one or more components, i.e. antioxidant, can be employed while reducing the amount of another component of the same type or having a similar type of activity.

The invention will now be further illustrated by the following example.

EXAMPLE 1

A topical composition including a mixture of an hydrophilic ointment base, sodium acid phosphate moisturizing agent, witch hazel extract, glycerine, apricot kernal oil and DL-panthenol, formulated together as the pharmaceutically acceptable carrier, and further including, as active agents, vitamins A and D_3, ascorbyl palmitate, quercetin and vitamin E acetate, was prepared by cold compounding. The formulation of the composition is given in Table 1.

The composition was prepared by first placing the hydrophilic ointment base in a stainless steel bowl and mixing briskly until the ointment becomes creamy. Then, the sodium acid phosphate, panthenol, ascorbyl palmitate, glycerine, apricot kernal oil, vitamins A and D_3, witch hazel extract, vitamin E acetate and quercetin are added in that order. After each ingredient is added, mixing is continued until all traces of dry ingredients have disappeared and a substantially homogeneous mixture is obtained. The final color should be a consistent yellow and the cream should have the consistency of cake frosting. The mixture is then placed in a sterile container. All containers, which contact the composition during mixing must also be sterilized with, for example, zephiran choride or a chlorox solution such as betadine.

This composition was topically administered, under the supervision of a physician, to several patients diagnosed with the most difficult cases of diabetic peripheral neuropathy. The topical composition was applied twice daily in the morning and afternoon, except that patients were permitted to apply the composition up to six times daily, as needed for pain relief over a period of a few days. All of the eight patients treated experienced immediate positive results that lasted up to a day or two after treatment was discontinued. The effects noted by the patients included the relief of burning pain, tingling, healing of damaged skin, and reversal of skin discoloration due to impaired circulation.

Table 1

Ingredient	Amount Employed
Hydrophilic ointment base	1 pound
50% aqueous solution of Sodium acid phosphate	25 cc
DL-panthenol	5 cc
Glycerine	5 cc
Apricot kernal oil	3 cc
Witch hazel extract	12 cc
Vitamin A and D_3 dispersion in corn oil	4 cc
Vitamin E acetate	1 cc
Ascorbyl Palmitate	2 grams
Quercetin powder	4 grams

The foregoing detailed description of the invention and examples are not intended to limit the scope of the invention in any way and should not be construed as limiting the scope of the invention. The scope of the invention is to be determined from the claims appended hereto.

What is claimed is:

1. A composition for the treatment of diabetic neuropathy including a mixture of an amount of one or more compounds that promote synthesis of nerve growth factor which is effective when administered in the composition to promote synthesis of nerve growth factor; an amount of one or more aldose reductase inhibitors which is effective when administered in the composition to inhibit aldose reductase; and an effective amount of one or more antioxidants.

2. The composition as claimed in claim 1, wherein the one or more compounds that promote synthesis of nerve growth factor are selected from: vitamin D_3, vitamin D_3 analogs, compounds that may be converted or metabolized into vitamin D_3 in the human body, metabolites thereof, and pharmaceutically acceptable salts thereof.

3. The composition as claimed in claim 1, wherein the one or more compounds that promote synthesis of nerve growth factor are selected from: vitamin D_3, 1, 25-dihydroxyvitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, and other vitamin D_3 derivatives which promote the synthesis of nerve growth factor, and pharmaceutically acceptable salts thereof.

4. The composition as claimed in claim 1, wherein the one or more antioxidants are selected from: ascorbyl palmitate, ascorbic acid, vitamin A, vitamin E acetate, α-lipoic acid, coenzyme Q10, glutathione, (-)-epigallocatechin-3-gallate, catechin, galangin, rutin, luteolin, morin, fisetin, silymarin, apigenin, gingkolides, hesperitin, cyanidin, citrin, curcuminoid, and structurally similar derivatives thereof which exhibit antioxidant activity, and pharmaceutically acceptable salts thereof.

5. The composition as claimed in claim 1, wherein the composition includes vitamin D_3, vitamin A, vitamin E acetate, and α-lipoic acid.

6. The composition as claimed in claim 1, wherein the one or more antioxidants include one or more antioxidant enzymes.

7. The composition as claimed in claim 1, wherein the one or more aldose reductase inhibitors are selected from: flavonoids, flavonoid derivatives which exhibit aldose reductase inhibiting properties, pharmaceutically acceptable salts thereof and mixtures thereof.

8. The composition as claimed in claim 7, wherein the one or more aldose reductase inhibitors are selected from: (-)-epigallocatechin; (-)-epigallocatechin-gallate; 1,2,3,6-tetra-o-gallyol-β-d-glucose; 2'o-acetylacetoside; 3,3',4-tri-o-methyl-ellagic acid; 6,3',4'-trihydroxy-5,7,8-trimethoxyflavone; 6-hydroxy-luteolin; 6-hydroxykaempferol-3,6-dimethyl ether; 7-o-acetyl-8-epi-loganic acid; acacetin; acetoside; acetyl trisulfate quercetin; amentoflavone; apigenin; apiin; astragalin; avicularin; axillarin; baicalein; brazilin; brevifolin carboxylic acid; caryophyllene; chrysin-5,7-dihydroxyflavone; chrysoeriol; chrysosplenol; chrysosplenoside-a; chrysosplenoside-d; cosmosiin; δ-cadinene; dimethylmussaenoside; diacerylcirsimaritin; diosmetin; dosmetin; ellagic acid; ebinin; ethyl brevifolin carboxylate; flavocannibiside; flavosativaside; genistein; gossypetin-8-glucoside; haematoxylin; hesperidine; hispiduloside; hyperin; indole; iridine; isoliquiritigenin; isoliquiritin; isoquercitrin; jionoside; juglanin; kaempferol-3-rhamnoside; kaempferol-3-neohesperidoside; kolaviron; licuraside; linariin; linarin; lonicerin; luteolin; luetolin-7-glucoside; luteolin-7-glucoside; luetolin-7-glucoronide; macrocarpal-a; macrocarpal-b; macrocarpal-d; macrocarpal-g; maniflavone; methy scutellarein; naringenin; naringin; nelumboside; nepetin; nepetrin; nerolidol; oxyayanin-a; pectolinarigenin; pectolinarin; quercetagetin; quercetin; quercimertrin; quercitrin; quercitryl-2'' acetate; reynoutrin; rhamnetin; rhoifolin; rutin; scutellarein; sideritoflavone; sophoricoside; sorbarin; spiraeoside; trifolin; vitexin; and wogonin; and pharmaceutically acceptable salts thereof.

9. The composition as claimed in claim 7, wherein the one or more aldose reductase inhibitors include at least one compound selected from: quercetin, quercitrin, myricetin, kaempferol and myrecetrin.

10. The composition as claimed in claim 1, wherein the one or more antioxidants include a mixture of at least two different compounds.

11. The composition as claimed in claim 1, wherein the one or more antioxidants include vitamin E acetate.

12. The composition as claimed in claim 1, wherein the one or more antioxidants include vitamin A.

13. The composition as claimed in claim 1, wherein the one or more antioxidants include ascorbyl palmitate.

14. The composition as claimed in claim 13, wherein the one or more antioxidants further include at least one compound selected from: vitamin E acetate and vitamin A.

15. The composition as claimed in claim 1, wherein the one or more compounds that promote synthesis of nerve growth factor include vitamin D_3.

16. The composition as claimed in claim 15, wherein the one or more antioxidants include at least one compound selected from: vitamin A, vitamin E acetate, and ascorbyl palmitate.

17. The composition as claimed in claim 15, wherein the one or more antioxidants include vitamin A, vitamin E acetate and ascorbyl palmitate and the one or more aldose reductase inhibitors comprise quercetin.

18. The composition as claimed in any one of claims 1-17, further including a pharmaceutically acceptable carrier.

19. The composition as claimed in claim 18, wherein the pharmaceutically acceptable carrier includes a sufficient amount of at least one non-U.S.P. hydrophilic ointment base to form a substantially topical composition.

20. The composition as claimed in claim 19, wherein the pharmaceutically acceptable carrier further includes a sufficient amount of a panthenol selected from D-panthenol and DL-panthenol to promote penetration of one or more compounds of the composition into the skin.

21. The composition as claimed in claim 18, wherein the pharmaceutically acceptable carrier includes hydroxymethyl cellulose.

22. The composition as claimed in claim 18, wherein the pharmaceutically acceptable carrier comprises an acrylic copolymer dissolved in polyethylene glycol.

23. A method of treating diabetic neuropathy comprising the step of administering by a method of administration selected from topical administration, oral administration, parenteral administration and inhalation,

an effective amount of a mixture which comprises an amount of one or more compounds that promote synthesis of nerve growth factor which is effective, when administered in the composition, to promote synthesis of nerve growth factor;

an amount of one or more aldose reductase inhibitors which is effective, when administered in the composition, to inhibit aldose reductase; and

an effective amount of one or more antioxidants.

24. The method as claimed in claim 23, wherein the one or more compounds that promote synthesis of nerve growth factor are selected from: vitamin D_3, vitamin D_3 analogs, compounds that may be converted or metabolized into vitamin D_3 in the human body, and metabolites thereof.

25. The method as claimed in claim 23, wherein the one or more compounds that promote synthesis of nerve growth factor are selected from: vitamin D_3, 1, 25-dihydroxyvitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, and other vitamin D_3 derivatives which promote the synthesis of nerve growth factor, pharmaceutically acceptable salts thereof and mixtures thereof.

26. The method as claimed in claim 23, wherein the one or more antioxidants are selected from: ascorbyl palmitate, ascorbic acid, vitamin A, vitamin E acetate, α-lipoic acid, coenzyme Q10, glutathione, (-)-epigallocatechin-3-gallate, catechin, galangin, rutin, luteolin, morin, fisetin, silymarin, apigenin, gingkolides, hesperitin, cyanidin, citrin, curcuminoid, and structurally similar derivatives thereof which exhibit antioxidant activity, and pharmaceutically acceptable salts thereof.

27. The method as claimed in claim 23, wherein the one or more compounds that promote synthesis of nerve growth factor include vitamin D_3, and the one or more antioxidants comprise vitamin A, vitamin E acetate, and α-lipoic acid.

28. The method as claimed in claim 23, wherein the one or more antioxidants include one or more antioxidant enzymes.

29. The method as claimed in claim 23, wherein the one or more aldose reductase inhibitors are selected from: flavonoids, flavonoid derivatives which exhibit aldose

reductase inhibiting properties, pharmaceutically acceptable salts thereof and mixtures thereof.

30. The method as claimed in claim 29, wherein the one or more aldose reductase inhibitors are selected from: (-)-epigallocatechin; (-)-epigallocatechin-gallate; 1,2,3,6-tetra-o-gallyol-β-d-glucose; 2'o-acetylacetoside; 3,3',4-tri-o-methyl-ellagic acid; 6,3',4'-trihydroxy-5,7,8-trimethoxyflavone; 6-hydroxy-luteolin; 6-hydroxykaempferol-3,6-dimethyl ether; 7-o-acetyl-8-epi-loganic acid; acacetin; acetoside; acetyl trisulfate quercetin; amentoflavone; apigenin; apiin; astragalin; avicularin; axillarin; baicalein; brazilin; brevifolin carboxylic acid; caryophyllene; chrysin-5,7-dihydroxyflavone; chrysoeriol; chrysosplenol; chrysosplenoside-a; chrysosplenoside-d; cosmosiin; δ-cadinene; dimethylmussaenoside; diacerylcirsimaritin; diosmetin; dosmetin; ellagic acid; ebinin; ethyl brevifolin carboxylate; flavocannibiside; flavosativaside; genistein; gossypetin-8-glucoside; haematoxylin; hesperidine; hispiduloside; hyperin; indole; iridine; isoliquiritigenin; isoliquiritin; isoquercitrin; jionoside; juglanin; kaempferol-3-rhamnoside; kaempferol-3-neohesperidoside; kolaviron; licuraside; linariin; linarin; lonicerin; luteolin; luetolin-7-glucoside; luteolin-7-glucoside; luetolin-7-glucoronide; macrocarpal-a; macrocarpal-b; macrocarpal-d; macrocarpal-g; maniflavone; methy scutellarein; naringenin; naringin; nelumboside; nepetin; nepetrin; nerolidol; oxyayanin-a; pectolinarigenin; pectolinarin; quercetagetin; quercetin; quercimertrin; quercitrin; quercitryl-2'' acetate; reynoutrin; rhamnetin; rhoifolin; rutin; scutellarein; sideritoflavone; sophoricoside; sorbarin; spiraeoside; trifolin; vitexin; and wogonin; and pharmaceutically acceptable salts thereof.

31. The method as claimed in claim 29, wherein the one or more aldose reductase inhibitors include at least one compound selected from: quercetin, quercitrin, myricetin, kaempferol and myrecetrin.

32. The method as claimed in claim 23, wherein the one or more antioxidants include a mixture of at least two different compounds.

33. The method as claimed in claim 23, wherein the one or more antioxidants include vitamin E acetate.

34. The method as claimed in claim 23, wherein the one or more antioxidants include vitamin A.

35. The method as claimed in claim 23, wherein the one or more antioxidants include ascorbyl palmitate.

36. The method as claimed in claim 35, wherein the one or more antioxidants further include at least one compound selected from: vitamin E acetate and vitamin A.

37. The method as claimed in claim 23, wherein the one or more compounds that promote the synthesis of nerve growth factor include vitamin D_3.

38. The method as claimed in claim 37, wherein the one or more antioxidants include at least one compound selected from: vitamin A, vitamin E acetate, and ascorbyl palmitate.

39. The method as claimed in claim 38, wherein the one or more antioxidants include vitamin A, vitamin E acetate and ascorbyl palmitate and the one or more aldose reductase inhibitors comprise quercetin.

40. The method as claimed in any one of claims 23-39, wherein the composition further includes a pharmaceutically acceptable carrier.

41. The method as claimed in claim 40, wherein the carrier is a topical carrier and the method of administration is topical administration.

42. The method as claimed in claim 41, wherein the pharmaceutically acceptable topical carrier includes a sufficient amount of at least one non-U.S.P. hydrophilic ointment base to form a substantially topical composition.

43. The method as claimed in claim 42, wherein the pharmaceutically acceptable topical carrier further includes a sufficient amount of a panthenol selected from D-panthenol and DL-panthenol to promote penetration of the composition into skin.

44. The method as claimed in claim 41, wherein the pharmaceutically acceptable carrier includes hydroxymethyl cellulose.

45. The method as claimed in claim 41, wherein the pharmaceutically acceptable topical carrier includes an acrylic copolymer dissolved in polyethylene glycol.